

UNRAVELING DEGENERATIVE BRAIN DISORDERS

A Case for Sweat, Genius and Serendipity

BY IDELLE DAVIDSON

JUST AS THERE ARE BILLIONS OF STARS IN OUR solar system, so too are there billions of cells in the human brain. The neuroscientists at Cedars-Sinai Medical Center who explore these cellular frontiers to understand brain diseases are, in a sense, astronomers of a vast and complex biological universe, with genetics as their navigational system.

Stefan M. Pulst, MD, is an internationally known expert in movement disorders. He is director of the Division of Neurology and holder of the Carmen and Louis Warschaw Chair in Neurology.

Behind the gentle demeanor of this physician, who wears paisley bow ties with his lab coats, is a tenacious and highly accomplished scientist. “It is what you do with your life that matters,” he says. “What I care about is curing degenerative diseases.”

That includes Parkinson’s disease, Alzheimer’s disease, spastic paraplegias, and Lou Gehrig’s disease, or ALS. “The unsolved question is ‘How do we stop the premature death of nerve cells?’”

says Dr. Pulst, who has authored five books on neurogenetics.

It all begins with families. Dr. Pulst and his staff study and treat inherited disorders of the nervous system. First they track the mutant gene in family members, then they map the gene to a particular chromosome. “From there we work our way back,” he says. “We want to know the function of this causative gene, what happens to it when it has mutated.”

The team has located three genes that cause movement disorders, or ataxias—vicious, brain-destroying diseases that ravage coordination and often strike individuals with dementia. All are dominant diseases: Those carrying one copy of the mutated gene will likely develop a disease. Their children are at 50 percent risk. Dr. Pulst’s group discovered three of the 15 genes responsible for spinocerebellar ataxia (SCA).

Cedars-Sinai scientists have developed blood tests to screen for these three SCAs. They can now rule out other disorders with similar characteris-

tics, such as multiple sclerosis. Research has moved forward, but there is still no cure. “Even finding a treatment to ameliorate the symptoms would be a major breakthrough,” says Dr. Pulst.

At least now we know the enemy. One is a mutated gene called SCA2, discovered by Dr. Pulst’s team a decade ago. Researchers had known for years that a particular form of ataxia targeted Cuban populations. But it was Pulst’s group that connected the disease with the gene. “It is actually so common in Cuba that it is a public health problem there,” says Pulst. Cuban doctors now

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offer rehabilitation programs and prenatal diagnosis.

They discovered that the same mutated gene was also associated with Parkinson’s disease in some families. Parkinson’s is characterized by severe tremors, rigidity in the limbs, and the loss of muscle control. Although its cause is unknown, the disease results from the death of brain cells that produce a critical brain chemical called dopamine. Symptoms worsen as more cells die. The National Institutes of Health has funded the Pulst lab to identify how parkin—a gene and protein involved in Parkinson’s disease—degrades other proteins involved in the disease. “We have found that these proteins are interacting partners of parkin,” says Dr. Pulst. “Two are proteins involved in neurotransmitter release and the third was our old friend, SCA2. This is an important step in linking different movement disorders at the molecular level.”

FOR DR. PULST, THE STUDY OF GENETICS IS akin to opening an oyster: Sometimes you find a treasure. That is what happened three years ago, when Pulst examined the DNA from a family with a novel form of ataxia. Michael F. Waters, MD, PhD, identified the gene KCNC3 while working with Pulst as a neurogenetics fellow. Dr. Waters is now director of the Cedars-Sinai Clinical Stroke Program (see article on page 20). Their findings were reported in *Nature Genetics*.

By studying two families with a history of ataxia, one Filipino and the other French, they found that although the KCNC3 gene altered in both families, each family exhibited dramatically different symptoms. To their surprise, the two scientists learned that the KCNC3 mutation occurred in a protein that regulates the flow of potassium into nerve cells. In the French family, the potassium-ion

channel remained open. The neurons worked, but not correctly. Yet in the Filipino family, the potassium-ion channel did not work at all.

“This was a remarkable find,” says Dr. Pulst. “Although mutations in these types of proteins are known to occur in patients with epilepsy, this was the first time we had seen them in neurodegenerative diseases. We are now looking for changes in other ion channels.” The NIH is supporting their work with a translational research grant. By evaluating novel chemical compounds that target ion channels, they hope to eventually develop treatments for Alzheimer’s and Parkinson’s diseases, and especially ataxias. ●

